Understanding the need for paediatric DR-TB formulations in South Africa

S Harichander, BPharm, MHS; **V Bangalee**, BPharm, MPharm, PhD; **F Oosthuizen**, BPharm, PhD

Discipline of Pharmaceutical Sciences, School of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

Corresponding author: *S Harichander (sheetal.harichander@gmail.com)*

In recent years, significant advancements have been made in the management of drug-resistant (DR) tuberculosis (TB), including the use of new and repurposed drugs. Research has primarily focused on adults as only a small number of children are diagnosed and treated for DR-TB annually, often making them the last group to benefit from these developments. This perspective aims to describe the availability of child-friendly formulations for treating DR-TB in South Africa. Developing and providing child-friendly formulations is essential to addressing the unique challenges of managing DR-TB in children, ensuring appropriate dosing, tolerability and adherence to treatment regimens. This is a crucial step to improving treatment outcomes and reducing the global burden of DR-TB.

Keywords. paediatrics; drug resistance; tuberculosis; dosage forms; treatment.

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Tuberculosis at a glance

Tuberculosis (TB) is a communicable disease and one of the leading causes of death worldwide.[1] Until the COVID-19 pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV and AIDS.[1]

Drug-resistant (DR) TB poses a significant global challenge to TB care and prevention, making the disease harder and longer to treat, often resulting in poorer patient outcomes.[2] However, cure is possible with early identification of resistance and a properly designed regimen.[2] Children and adolescents, particularly those in households with DR-TB-infected adults, are highly susceptible to DR-TB.[3,4] Research estimates that between 25 000 and 32 000 children develop DR-TB annually, but less than 5% receive treatment.[5]

The spread of DR-TB has encouraged the development of new medicines and the reappraisal of older drugs that have seen little use in the last decade.[6-8] However, the lack of child-friendly formulations has delayed the alignment of treatment guidelines for children.[6-8] Traditionally, children have been treated based on data obtained from adults.[9] Providing access to suitable dosage forms for paediatric patients is a cornerstone of strategies to reduce the global burden of TB.[8] Children with DR-TB are particularly vulnerable and have often been the last to benefit from advances in both general paediatric care and DR-TB care.[8]

Though children with DR-TB have better treatment outcomes than adults,[7,8] many children struggle during the treatment owing to the limited availability of paediatric formulations of anti-tubercular medication.[9] In South Africa (SA), only linezolid (LZD) is available in a liquid formulation and p-amino salicylic acid (PAS) as a granule, while all other drugs are available only as tablets and capsules. The limited availability of oral liquids and dosage forms given by alternative routes means that dissolving tablets and emptying capsules is common practice for the treatment of DR-TB in children, as healthcare professionals (HCPs) and caregivers must manipulate the dosage form when administering to children who cannot swallow tablets and capsules.[10] Paediatric patients have traditionally been treated with off-label adult pharmaceuticals or extemporaneous compounding, which is not optimal owing to a lack of product safety and efficacy information.[11] This perspective aims to describe the availability and necessity of child-friendly formulations to treat DR-TB in SA.

Challenges in the management of DR-TB in children

While treatment outcomes for most TB types including DR-TB in children are notably favourable, there remains a low uptake of treatment owing to difficulties in identifying cases and promptly diagnosing the disease.[9] Despite recent progress in rapid diagnostics, achieving a microbiological diagnosis of children patients continues to pose challenges.[10] The children encounter difficulties in producing sputum and may present with paucibacillary illnesses, thereby reducing the effectiveness and reliability of current TB detection laboratory tests.[10]

The administration of medicines to paediatric patients has been a challenge for parents/caregivers and HCPs. The lack of age-appropriate dosage forms for children contributes to this problem.[11,12] This compels parents/caregivers and HCPs to manipulate dosage forms to get the appropriate dose or to make the administration possible.[11,12] In a clinical setting, manipulation occurs frequently, either within the pharmacy in the preparation of extemporaneous medicines or the wards at the point of administration.[13]

Table 1 details the characteristics of available second-line anti-tubercular drugs for the management of DR-TB in children.[7,14-16]

There are problems associated with the manipulation of dosage forms, such as the possibility of under- or overdosing a patient.[17,18] Besides the possible negative effects on dose accuracy, manipulating the drug's dosage forms could negatively impact the stability, solubility and bioavailability.[17,18] Many manipulated drugs also have a strong, unpleasant taste, often causing children to reject or spit out the medication, further complicating adherence and risking treatment failure.[19] In most cases, manipulation of dosage forms is used off-label. Therefore, the manufacturer will not bear any responsibility for any harm to the patient after manipulating a pharmaceutical dosage form.

Table 1. Characteristics of available second-line antitubercular drugs for management of DR-TB in children

WHO Group	Drug	Dosage forms registered for use in SA	Palatability of manipulated preparations	Availability of child-friendly formulation
A Include all three medicines, where possible	Levofloxacin	250 mg film-coated scored tablet 500 mg film-coated scored tablet 750 mg film-coated scored tablet	Bitter taste	100 mg dispersible tablet Available from Stop TB Partnership Global Drug Facility
	or			
	Moxifloxacin	400 mg tablet	Bitter taste	100 mg dispersible tablet Available from Stop TB Partnership Global Drug Facility
	Bedaquiline	100 mg uncoated tablet	Palatable	20 mg dispersible tablet Available from Stop TB Partnership Global Drug Facility
	Linezolid	600 mg tablet 20 mg/mL suspension	Bitter taste Orange flavoured	20 mg/mL suspension (registered in SA) 150 mg dispersible tablet Available from Stop TB Partnership Global Drug Facility
B Add one or both medicines, if possible	Clofazimine	100 mg capsule	Bitter taste	50 mg dispersible tablet 50 mg capsule Available from Stop TB Partnership Global Drug Facility
	Terizidone	250 mg capsule	Bitter taste	No child-friendly formulations available
C Add to complete the regimen and when medicines from Group A and B cannot be used	Ethambutol	400 mg tablet	Bitter taste	25 mg/mL tablet 100 mg dispersible tablet Available from Stop TB Partnership Global Drug Facility
	Delamanid	50 mg film-coated tablet	Bitter taste	25 mg dispersible tablet Available from Stop TB Partnership Global Drug Facility
	Pyrazinamide	500 mg uncoated scored tablet	Not assessed	100 mg dispersible tablet Available from Stop TB Partnership Global Drug Facility
	Amikacin	IV, IM	Not applicable	No child-friendly formulations available
	Ethionamide	250 mg film-coated tablet	Bitter taste	125 mg dispersible tablet Available from Stop TB Partnership Global Drug Facility
	Para-aminosalicylic acid	4 g coated granule	Bitter taste	No child-friendly formulations available

DR = drug-resistant; TB = tuberculosis; WHO = World Health Organization; SA = South Africa; IV = intravenous; IM = intramuscular.

The burden of caring

Caregivers and nurses face challenges in managing the treatment of children with DR-TB. Nurses play a crucial role in ensuring patient safety, bearing the unique responsibility of verifying the accuracy of prescribed and dispensed medications before administration. Typically, nurses in paediatric wards manipulate medication dosage forms within medication rooms. Manipulation of dosage forms is time-consuming and heightens the risk of errors, especially since drug calculation errors are the most common in paediatric practice.[12] Therefore, standardising procedures is essential to reduce the risks associated with manipulating dosage forms. Nurses require constant support and training from prescribing doctors and pharmacists to manipulate dosage forms effectively. In addition, nurses are responsible for providing education to caregivers of children with DR-TB about the condition, medication, administration techniques, potential adverse drug reactions and the importance of medication adherence.

Caregivers are often tasked with medication preparation and administration for the children at home. This is a complex process

that involves multiple drugs, which can be challenging for caregivers to manage effectively.[20,21] Many of these drugs are toxic and can cause adverse reactions, which can be distressing for caregivers.[20,21] The main challenge lies in preparing accurate doses, which often requires dissolving tablets, opening capsules or breaking tablets—a time-consuming and difficult task.[20,21] Caregivers often face challenges such as the poor palatability of medications, requiring coercion to ensure children adhere to therapy.[20,21] Caregivers may experience emotional stress and burnout owing to the challenges of caring for a loved one with DR-TB, including concerns about treatment effectiveness and the long-term prognosis.[20,21]

Many caregivers have reported that drug compounding is a difficult process, and HCPs frequently express uncertainty about the quality and accuracy of the doses prepared at home by the caregivers.

A turning point in paediatric DR-TB

In recent times, there has been a gradual increase in the availability of child-friendly formulations of second-line TB drugs.[15,22] The Stop TB Partnership's Global Drug Facility (GDF), the largest global supplier of quality-assured TB drugs, has made efforts to incorporate child-friendly formulations for drugs such as bedaquiline, clofazimine, cycloserine/terizidone, ethambutol, ethionamide, levofloxacin, moxifloxacin and pyrazinamide in their product range.[15,22] In collaboration with the Sentinel Project, they have also supported the global uptake of these formulations.[15,22] However, in some countries, including the European Union and SA, these formulations remain unapproved and inaccessible. Countries with access should prioritise their procurement.[23]

These innovative new formulations were designed as dispersible tablets in lower doses to ensure more accurate dosing and simpler administration. While not novel drugs, these dosage forms of existing medications were designed to improve the treatment of children with DR-TB. These new formulations are not registered in SA and an application for permission to use an unregistered product in the country had to be made to the South African Health Products Regulatory Authority (SAHPRA).[24] The KwaZulu-Natal (KZN) province applied to the GDF for donation supplies of these child-friendly formulations, which were to be managed at King Dinuzulu Hospital Complex.[24] In 2020, KZN received dispersible tablets of ethambutol 100 mg, pyrazinamide 150 mg and levofloxacin.[24] In 2021, dispersible clofazimine 50 mg was also received.[24] These formulations are currently being used in the Eastern and Western Cape provinces as well.

Paving the way forward

Despite being a high-burden DR-TB country, SA has faced widening gaps in care following the COVID-19 pandemic, with fewer patients tested, diagnosed and successfully treated. Efforts must now focus on identifying undiagnosed cases, ensuring appropriate treatment, and building evidence to advocate for a sustainable supply of child-friendly formulations.

The development and availability of child-friendly formulations for all second-line DR-TB medications is essential. These should include dispersible tablets, palatable liquids and age-appropriate fixed-dose combinations. Pharmaceutical companies and regulatory agencies can be engaged to expedite the approval and production of these formulations.

Access to DR-TB diagnosis and treatment for children, particularly in resource-limited settings, should be improved. Improving access would involve strengthening healthcare systems, increasing the availability of paediatric TB services and reducing financial barriers to care through initiatives such as subsidised treatment and social support programmes. Integrating TB care with existing maternal and child health services can facilitate early detection and ensure comprehensive management of paediatric TB cases. This includes incorporating TB screening and treatment into routine paediatric healthcare visits and leveraging existing platforms, such as immunisation programmes and child welfare clinics, to enhance early detection and care.

Although new second-line drugs for DR-TB have been approved for paediatric use, access to these treatments remains challenging in many countries. More effort should be directed towards ensuring the accessibility of currently available child-friendly formulations nationally.

By implementing these strategies and engaging in collaborative efforts, we can effectively address DR-TB in children, improve treatment outcomes and ultimately reduce the global burden of paediatric TB.

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1. Medecins Sans Frontieres, Tuberculosis, https://medicalguidelines.msf.org/viewport/TUB/latest/introduction-20320166.html (accessed 19 January 2021).
2. World Health Organization. Global Tuberculosis Report, 2022.
3. Rasanathan K, Sivasankara Kurup A, Jaramillo E, Lönnroth K. The social determinants of health: Key to global tuberculosis control. Int J Tubercul Lung Dis 2011;15 (6):S30-S36. https://doi.org/10.5588/ijtld.10.0691
4. World Health Organization. Health topics. Tuberculosis. 2023. https://www.who.int/health-topics/tuberculosis#tab=tab_1 (accessed 21 September 2023).
5. D'Ambrosio L, Centis R, Tiberi S, et al. Delamanid and bedaquiline to treat multidrug-resistant and extensively drug-resistant tuberculosis in children: A systematic review. J Thoracic Dis 2017;9(7):2093-2101. https://doi.org/10.21037/jtd.2017.06.16
6. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: Early experiences and challenges. Eur Respir J 2016;48(3):938-943. https://doi.org/10.1183/13993003.00705-2016
7. Buonsenso D, Autore G, Cusenza F, Passadore L, Bonanno F, Esposito S. Multidrug-resistant tuberculosis in children: Are the same therapy options available worldwide? Int J Infect Dis 2023;130:S16-S19. https://doi.org/10.1016/j.ijid.2023.03.023
8. Huynh J, Thwaites G, Marais BJ, Schaaf HS. Tuberculosis treatment in children: The changing landscape. Paediatric Respir Rev 2020;36:33-43. https://doi.org/10.1016/j.prrv.2020.02.002
9. Harichander S, Wiafe E, Mensah KB, Bangalee V, Oosthuizen F. The incidence of TB and MDR-TB in pediatrics and therapeutic options: A systematic review. Systematic Rev 2022;11(1):157. https://doi.org/10.1186/s13643-022-02023-1
10. Ketema W, Woubishet K, Tesfaye S, et al. A breakthrough in the challenges of tuberculosis diagnosis: Lateral flow urine lipoarabinomannan (LAM) assay for the diagnosis of active tuberculosis in a subset of human immunodeficiency virus (HIV) patients at Hawassa University Comprehensive Specialised Hospital, Hawassa, Ethiopia. Int Med Case Rep J 2022;15:393-397. https://doi.org/10.2147/imcrj.s373197
11. van Riet-Nales DA, de Jager KE, Schobben AF, Egberts TC, Rademaker CM. The availability and age-appropriateness of medicines authorised for children in The Netherlands. Br J Clin Pharmacol 2011;72(3):465-473. https://doi.org/10.1111/j.1365-2125.2011.03982.x
12. Richey RH, Shah UU, Peak M, et al. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. BMC Pediatrics 2013;13:1-8. https://doi.org/10.1186/1471-2431-13-81
13. Walch AC, Henin E, Berthiller J, et al; EREMI Group. Oral dosage form administration practice in children under 6 years of age: A survey study of paediatric nurses. Int J Pharmaceutic 2016;511(2):855-863. https://doi.org/10.1016/j.ijpharm.2016.07.076
14. South African Medicines Formulary. 13th edition, 2020:325-340.
15. Stop TB Partnership Global Drug Facility. Medicines catalogue, 2024.
16. Wademan DT, Viljoen L, Jacobs S, et al. Children´s priorities to improve the acceptability of MDR-TB treatment: Qualitative data from South Africa. Int J Tubercul Lung Dis 2023;27(7):543-550. https://doi.org/10.5588/ijtld.22.0573

17. Martir J, Flanagan T, Mann J, Fotaki N. Impact of food and drink administration vehicles on paediatric formulation performance: Part 1-effects on solubility of poorly soluble drugs. AAPS PharmSciTech 2020;21(5):1-12. https://doi.org/10.1208/s12249-020-01722-z
18. McNeely EB, Talameh JA, Adams KF Jr, et al. Relative bioavailability of tolvaptan administered via nasogastric tube and tolvaptan tablets swallowed intact. Am J Health System Pharm 2013;70(14):1230-1237. https://doi.org/10.2146/ajhp120543
19. Ajayi TO, Poka MS, Witika BA. Nanotechnological innovations in paediatric tuberculosis management: Current trends and future prospects. Front Drug Delivery 2023;3:1295815. https://doi.org/10.3389/fddev.2023.1295815
20. Das M, Mathur T, Ravi S, et al. Challenging drug-resistant TB treatment journey for children, adolescents and their care-givers: A qualitative study. PLoS One 2021;16(3):e0248408. https://doi.org/10.1371/journal.pone.0248408
21. Misra S, Misra N, Seepamore B, et al. "I would watch her with awe as she swallowed the first handful": A qualitative study of pediatric multidrug-resistant tuberculosis experiences in Durban, South Africa. PLoS One 2022;17(9):e0274741. https://doi.org/10.1371/journal.pone.0274741
22. StopTB/GDF's Paediatric Drug-Resistant TB (DR-TB) Donation Initiative. 2021. http://sentinel-project.org/2019/02/18/stoptbgdfs-paediatric-drug-resistant-tb-dr-tb-donation-initiative/ (accessed 22 April 2023).
23. Howell P, Achar J, Huang GKL, Mariandyshev A, Schaaf HS, Garcia-Prats AJ. Treatment of rifampicin-resistant tuberculosis disease and infection in children: Key updates, challenges and opportunities. Pathogens 2022;11(4):381. https://doi.org/10.3390/pathogens11040381
24. Misra N. "We are the Children….Hear our Voices": Improving access to child-friendly formulations of drug resistance tuberculosis medicine: The KwaZulu-Natal experience. S Afr Pharm J 2023;90(6):56-58. https://hdl.handle.net/10520/ejc-mp_sapj_v90_n6_a10

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